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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/514,513	02/28/2000	Joseph Chappell	07678/011003	8901

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

[REDACTED] EXAMINER

KALLIS, RUSSELL

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1638

DATE MAILED: 07/30/2003

(B)

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/514,513 Examiner Russell Kallis	CHAPPELL ET AL. Art Unit 1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 January 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-15 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-15 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>12</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Drawings

CH 3 in Figure 6 shows the second active domain as having diagonal stripes when vertical stripes have been used to describe the active domain in the other sections of the figure.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
2. Claim 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims plant cells comprising nucleic acid molecules encoding a chimeric isoprenoid synthase having a non-naturally positioned or asymmetrically positioned functional domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase.

Applicant describes TEAS and HVS cDNA incorporated through reference (Back and Chappell, J. Biol. Chem. 1995, Vol. 270, pp. 7375); oligonucleotides of SEQ ID NO: 1-6 for

constructing chimeric synthases; domain maps of chimeric sesquiterpene synthases CH1-CH14 in Figure 4a comprising sections of TEAS and HVS; Figure 6 shows the domain switching strategy that produced CH4 and resulted in a synthase having an altered enzyme activity; Figures 7 and 8 show hypothetical domain switching and hypothetical reaction products for chimeric quiescent-casbene synthase and chimeric quiescent-cadinene synthase.

Applicant does not describe all chimeric isoprenoid synthases having asymmetrically positioned homologous domains that synthesizes any one or at least two of any possible kind of isoprenoid.

Given the claim breadth and lack of guidance as discussed above, the specification does not provide an adequate written description of the claimed invention.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

Based upon the disclosure of TEAS and HVS, there is insufficient relevant identifying characteristics to allow one skilled in the art to completely determine the structure of chimeric

isoprenoid synthases, that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, absent further guidance. Since the claimed genus encompasses undisclosed or yet to be discovered sequences that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, the disclosure TEAS, HVS and chimeric variants thereof, CH1-CH14, and quiescent synthases, does not provide adequate description of the broadly claimed genus. In view of the level of knowledge and skill in the art one skilled in the art would not recognize from Applicant's disclosure that Applicant was in possession of chimeric isoprenoid synthases having a non-naturally or asymmetrically positioned functional domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, other than chimeric variants of TEAS and HVS, (CH1-CH14), and quiescent synthases, as broadly claimed.

3. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plant cells and plants comprising chimeric variants of TEAS and HVS, (CH1-CH14), and quiescent synthases, does not reasonably provide enablement for plant cells and plants comprising any chimeric isoprenoid synthase having an asymmetrically positioned homologous domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant broadly claims plant cells and plants comprising nucleic acid molecules encoding a chimeric isoprenoid synthase having a non-naturally positioned or asymmetrically positioned functional domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, and the production of an antibacterial, antifungal, and antitumor agent thereof.

Applicant teaches TEAS and HVS cDNA incorporated through reference (Back and Chappell, J. Biol. Chem. 1995, Vol. 270, pp. 7375); oligonucleotides of SEQ ID NO: 1-6 for constructing chimeric synthases; domain maps of chimeric sesquiterpene synthases CH1-CH14 in Figure 4a comprising sections of TEAS and HVS; Figure 6 shows the domain switching strategy that produced CH4 and resulted in a synthase having an altered enzyme activity; Figures 7 and 8 show hypothetical domain switching and hypothetical reaction products for chimeric quiescent-casbene synthase and chimeric quiescent-cadinene synthase; cloning of CH1-CH14 using said oligonucleotides of SEQ ID NO: 1-6 on pages 10-16; altered aristolochene and vetispiradene ratios produced by CH4 and CH10-CH14 when transformed into E. coli on page 17 in Table 1; and the structure for potential chimeric quiescent synthases on pages 18-19; and potential chimeric casbene and cadiene synthases on pages 19-20; and prophetic transformation and expression of bacteria, yeast and plants using said chimeric synthases on pages 20-36.

Applicant does not teach all nucleic acid molecules encoding functional or nonfunctional domains of isoprenoid synthases that could be used as asymmetrically positioned homologous

domains in chimeric isoprenoid synthases other than the nucleic acid molecules encoding the functional domains from TEAS and HVS that when combined to form a chimera synthesize aristolochene and vetispiradene at various ratios (i.e. CH4 and CH10-CH14) when transformed into *E. coli*.

Designing chimeric proteins having modified catalytic function and altered products is highly unpredictable especially when changes are extrapolated onto similar enzymes that do not share the same biochemical mechanism. Without appropriate guidance, one of skill in the art would not know which domains when swapped would be effective. The unpredictability is evident in a newly defined group of monoterpene synthases, a sub group of the claimed isoprenoid synthases, isolated from snapdragon (Dudareva N. et al., *The Plant Cell*, May 2003, Vol. 15, p. 1227-1241; see page 1237 column 2 and page 1238 Figure 10). The isolated polynucleotides did not encode a conserved protein motif that is associated with the biochemical mechanism of the monoterpene synthases identified previously from other plant species and were lacking a 200 amino acid region common to the subfamily. Hence there appears to be a different mechanism at work in the monoterpene synthases isolated from snapdragon as compared to other species. Therefore, not all isoprenoid synthases are similar enough to allow for general assumptions in their redesign.

Given the unpredictability in the art as to which domains from which plants would tolerate chimerization; the breadth of the claims encompassing any plant cell comprising any number of enzymatic domains selected from a broad category of isoprenoid synthases; the lack of guidance in the specification or in the prior art as to which domains of the isoprenoid synthase enzyme family would best serve the invention; one would not know based upon Applicant's

Art Unit: 1638

disclosure which embodiments would be inoperable and predictably eliminated. Thus, undue trial and error experimentation would be needed to make and clone a multitude of non-exemplified isoprenoid synthase chimeras and to test them in a myriad of non-exemplified expression systems for a multitude of altered products that have either antifungal, antibacterial, or antitumoregenic activity. Therefore, the invention is not enabled for the scope set forth in the claims.

Art Unit: 1638

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Russell Kallis Ph.D.
July 25, 2003



AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600